

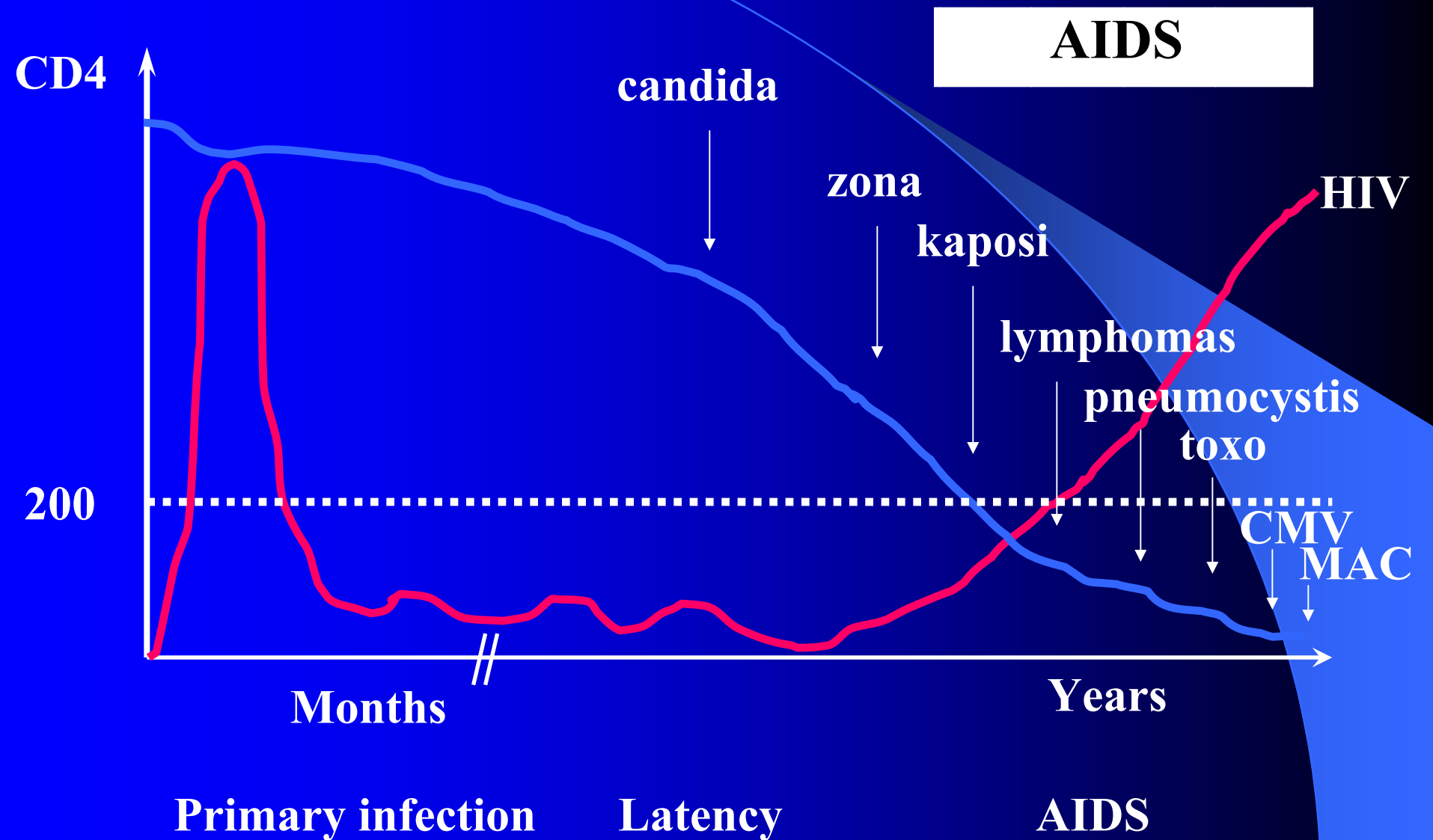
**Clinical outcomes and Immune
reconstitution after 12 months of HAART
in 103 Chinese HIV/AIDS patients**

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March 30 2006, Beijing

THE CD4 T CELL DEFECT LEADS TO AIDS



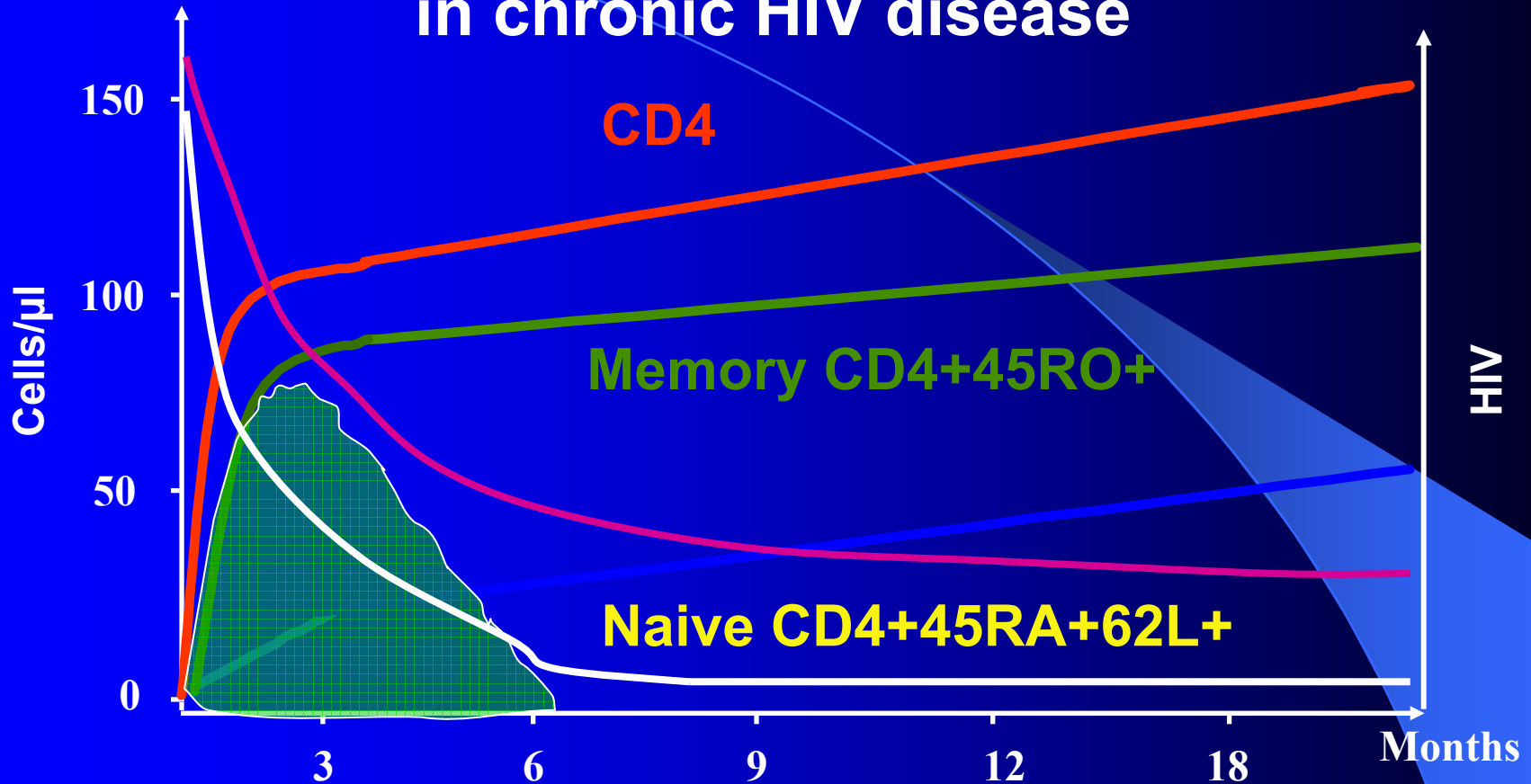
Natural evaluation of HIV infection

VL = 火车的速度

CD4 count = 离悬崖的距离



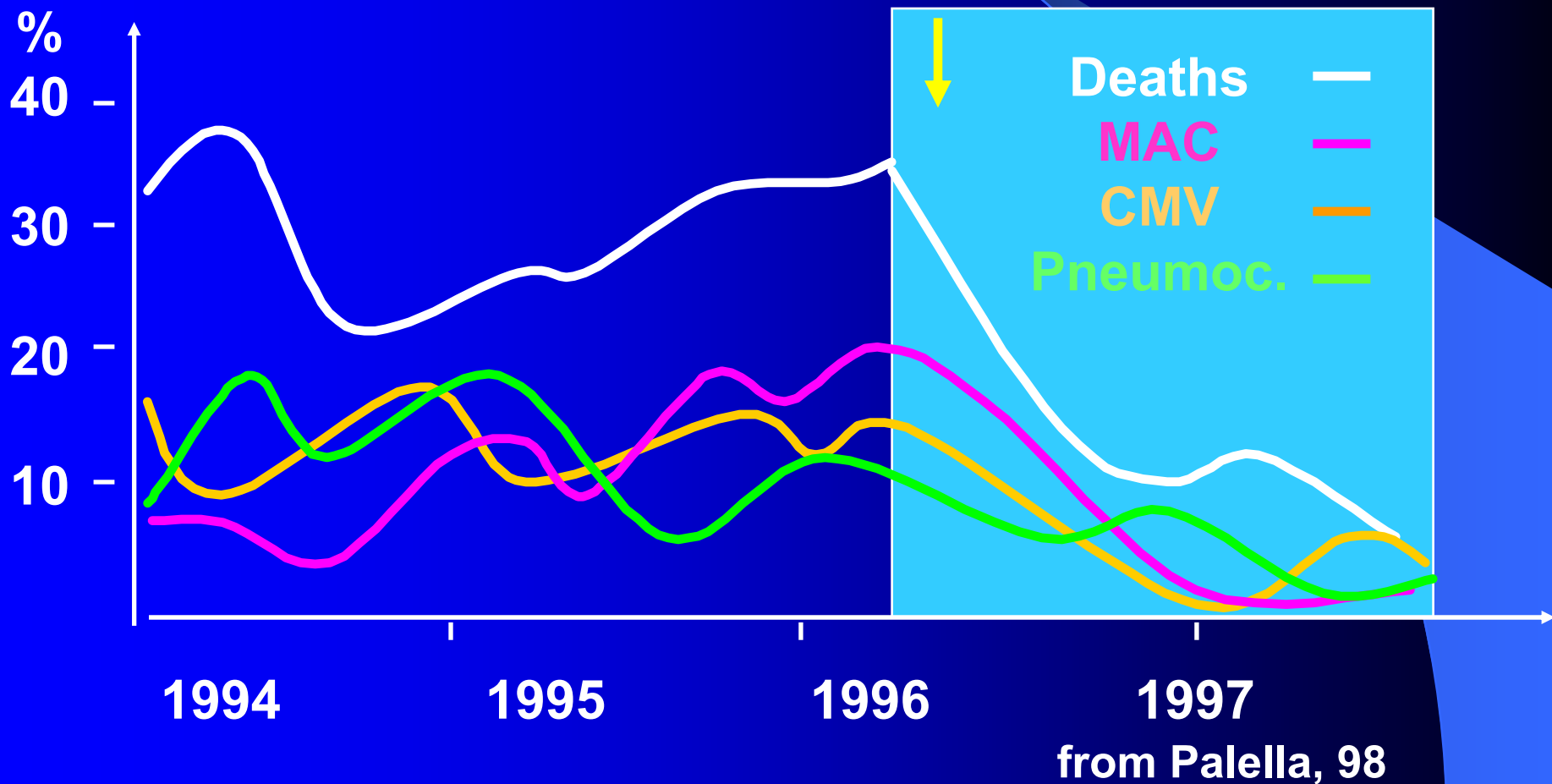
Effects of ART on the immune system in chronic HIV disease



- Early Memory CD4 T cell Redistribution
- Naive T cell regeneration > long term CD4 T cell expansion and
- Decreased T cell activation
- Re- diversification of T cell repertoires

(Autran 97, Pakker 98, Li 98, Lederman 98, Bucy 98, Gorochov 98....)

Reduced morbidity and mortality related to AIDS since HAART



卫生部公布艾滋病免费抗病毒治疗药品(附名录)

<http://www.rednet.com.cn> 2004-4-13 15:08:52 红网 中新网4月13日电

据央视国际消息，卫生部、财政部今天公布了艾滋病常见机会性感染名称和艾滋病免费抗病毒治疗药品名录。

常见机会性感染是指人体的免疫功能下降时，原本已经寄生在人体中一些非致病菌可以造成的疾病或者是对致病菌易感性增加所造成的感染，而这种感染对于一个具有正常免疫功能的人来说，不会造成疾病状态。

艾滋病常见机会性感染疾病是：细菌性感染中的：细菌性肺炎、细菌性肠炎、败血症、皮肤损伤、细菌性脑膜炎、结核、非结核分支杆菌感染。病毒性感染中的：CMV视网膜炎、单纯疱疹病毒感染、带状疱疹病毒感染。寄生虫感染中的：弓形体脑炎、隐孢子虫病。真菌感染中的：卡氏肺囊虫肺炎(PCP)、口腔和食道念珠菌感染、隐球菌脑膜炎。

中国艾滋病免费抗病毒治疗药品是：齐多夫定、司它夫定、去羟基苷、拉米夫定、奈维拉平、茚地那韦。

(稿源：中新网)
(编辑：胡蓉平)



一个由母婴渠道感染艾滋病的9岁女孩正在打吊针，这只能减缓她的一些并发病状，真正的救命药还是抗病毒“鸡尾酒”套餐。 柘城县双庙村一位村民的病情已经到了晚期，口腔内部已经出现霉菌感染，前来巡诊的张可医生将症状拍了下来，

●头疼头晕、视力模糊、四肢发麻、腹痛腹泻……是艾滋病感染者服用“鸡尾酒”套餐后的普遍反应，调查显示：目前河南地区有四成患者退出治疗。

●艾滋病感染者不规则用药带来“耐药性问题”，这成为卫生部门关注的一个新问题。专家对此表示忧虑：“一旦出现大面积耐药反应，我们将缺乏替代药物方案”。

●相关研究报告显示：中国病人发病时机偏晚。专家指出：这使得患者出现症状时免疫功能就已偏低，治疗时机被耽误。

Major problems for HIV/AIDS treatment in China now

- **The efficacy of H A A R T and toxicity for Chinese HIV/AIDS patients?**
- **Whiche combined ARV is better ? When we should initiate HAART?**
- **Immune reconstitution for Chinese AIDS patients, as well as the dynamics?**
- **Evalaution assay for HAART in China?**

Study aims

通过对接受规律HAART12个月的
HIV/AIDS患者的随访，探讨：

- **The efficacy and toxicity of ARV, as well as the immune reconstitution for Chinese HIV/AIDS patients;**
- **The relationship between TLC and CD4 T cell count before and after HAART;**
- **The relationship between CD8 activation subsets and HIV viral load before and after HAART;**

Study objectives

- ✦ HIV/AIDS Chinese adult patients;
- ✦ CD4+T cell count < 400/ul;
- ✦ Naïve to ARV;

■ Epidemiological information for patients

	Total	Group A (CD4 count <100/u1)	Group B (CD4 count \geq 100/u1)	
Number	103	69	34	
Sex (M: F)	58:45	38:31	15:19	
Age (Y)	38.2 \pm 12.9	39.7 \pm 16.5	37.3 \pm 11.0	
I Way	Blood	82	58	24
	Sex	15	7	8
	Unknow	5	4	1

A组：基线CD4T细胞计数<100/u1;

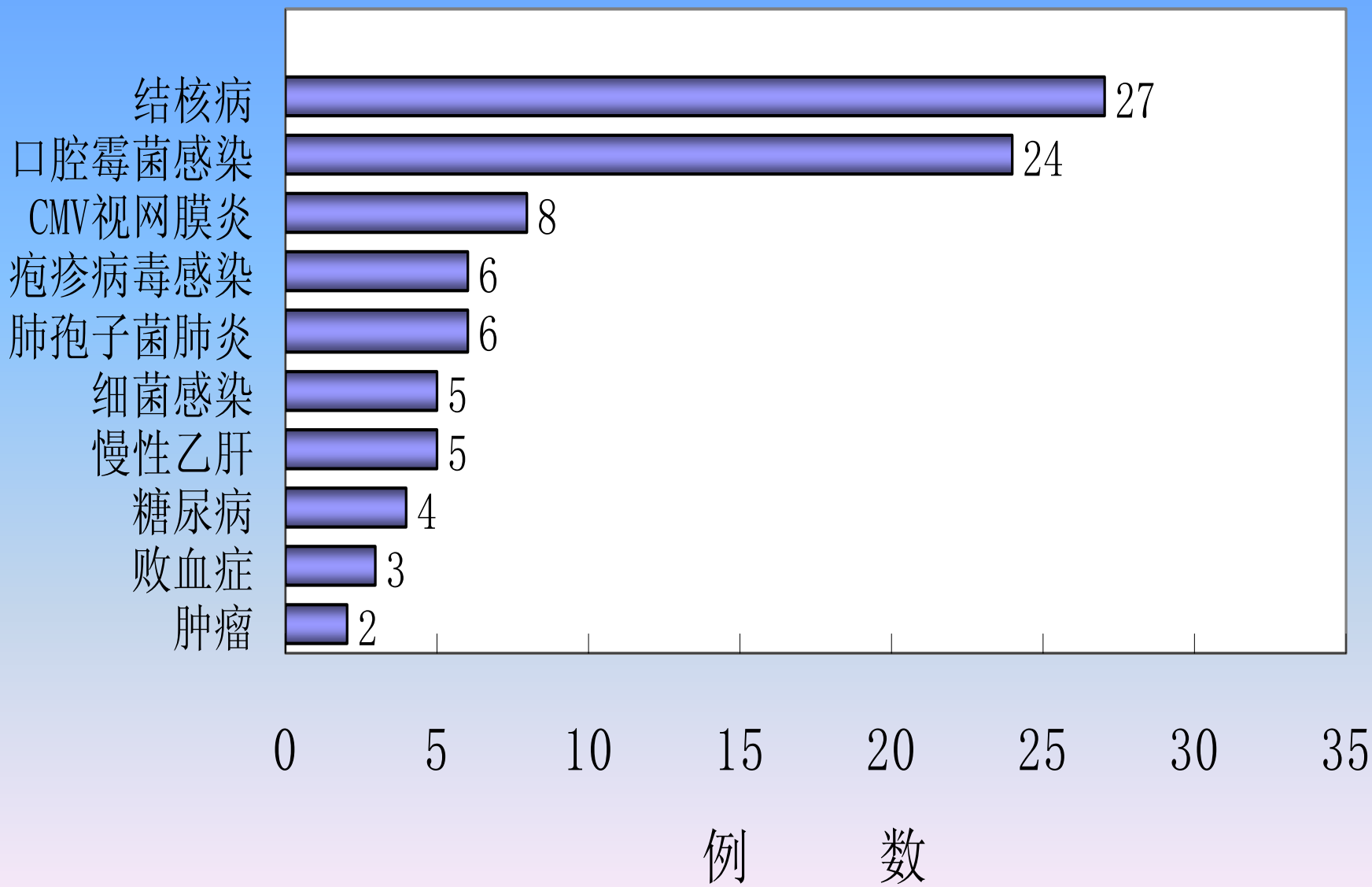
B组：基线CD4T细胞计数 \geq 100/u1。

Clinical characteristics of Patients

Phase*	Number
A2	10 (B组)
B2	9 (B组)
A3	15 (B组4例, A组11例)
B3	17 (B组7例, A组10例)
C1	2 (B组)
C2	2 (B组)
C3	48 (A组)

*临床分型按美国CDC (1993年) 诊断标准

103例患者基线时的合并症或机会性感染



入选患者基线指标

	Total (n=103)	A (n=69)	B (n=34)	P Value
TLC (/ul)	1085±473	810±443	1376±529	p=0.005
CD4T count(/ul)	106±85	52±38	264±191	P<0.001
CD8T count (/ul)	647±346	558±377	833±472	p=0.044
VL (Lg copies/ml)	5.215±0.811	5.410±0.738	5.015±1.022	p=0.052
Naïve CD4+T比例(%)	16.5±10.2	12.4 ± 6.6	26.3 ± 11.1	p=0.002
Memory CD4+T比例 (%)	73.8±21.0	78.2 ± 25.8	67.2 ± 13.5	P=0.008
CD4+CD28+T/CD4+T(%)	72.1±15.3	61.6 ± 18.4	87.6 ± 4.9	p<0.001
CD38+CD8+/ CD8+ (%)	85.7±9.28	90.2± 10.6	78.7 ± 8.8	p<0.001
DR+CD8+/ CD8+ (%)	52.2±13.0	59.4±21.7	43.9±15.6	p=0.001

Clinical improvemnet:

入选的103例HIV/AIDS患者经12个月HAART后，

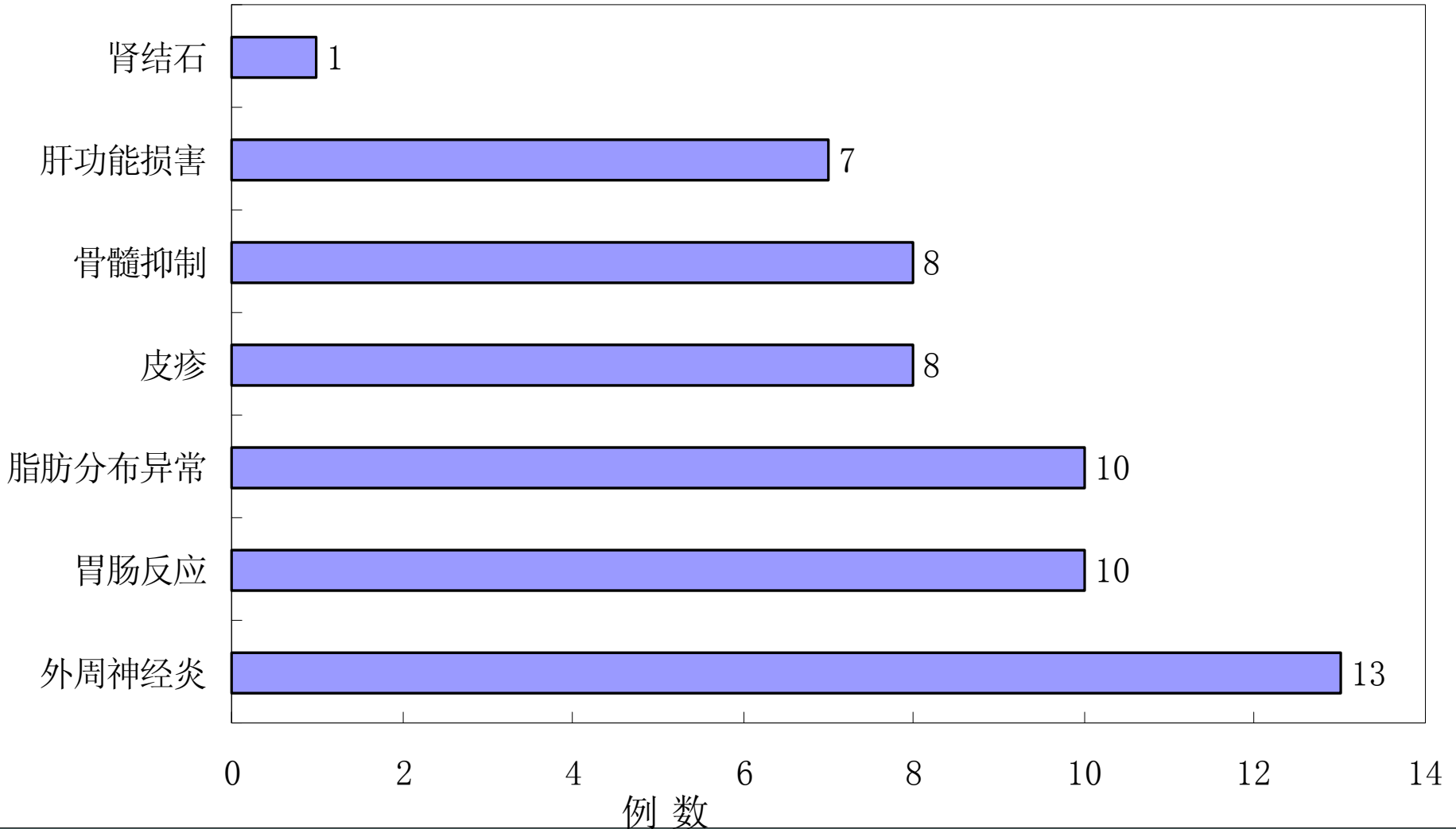
体力、精神状况等一般情况有不同程度改善，可从事正常体力活动

基线时所伴的机会性感染在HAART过程中都获得了稳定的控制，未见有复发

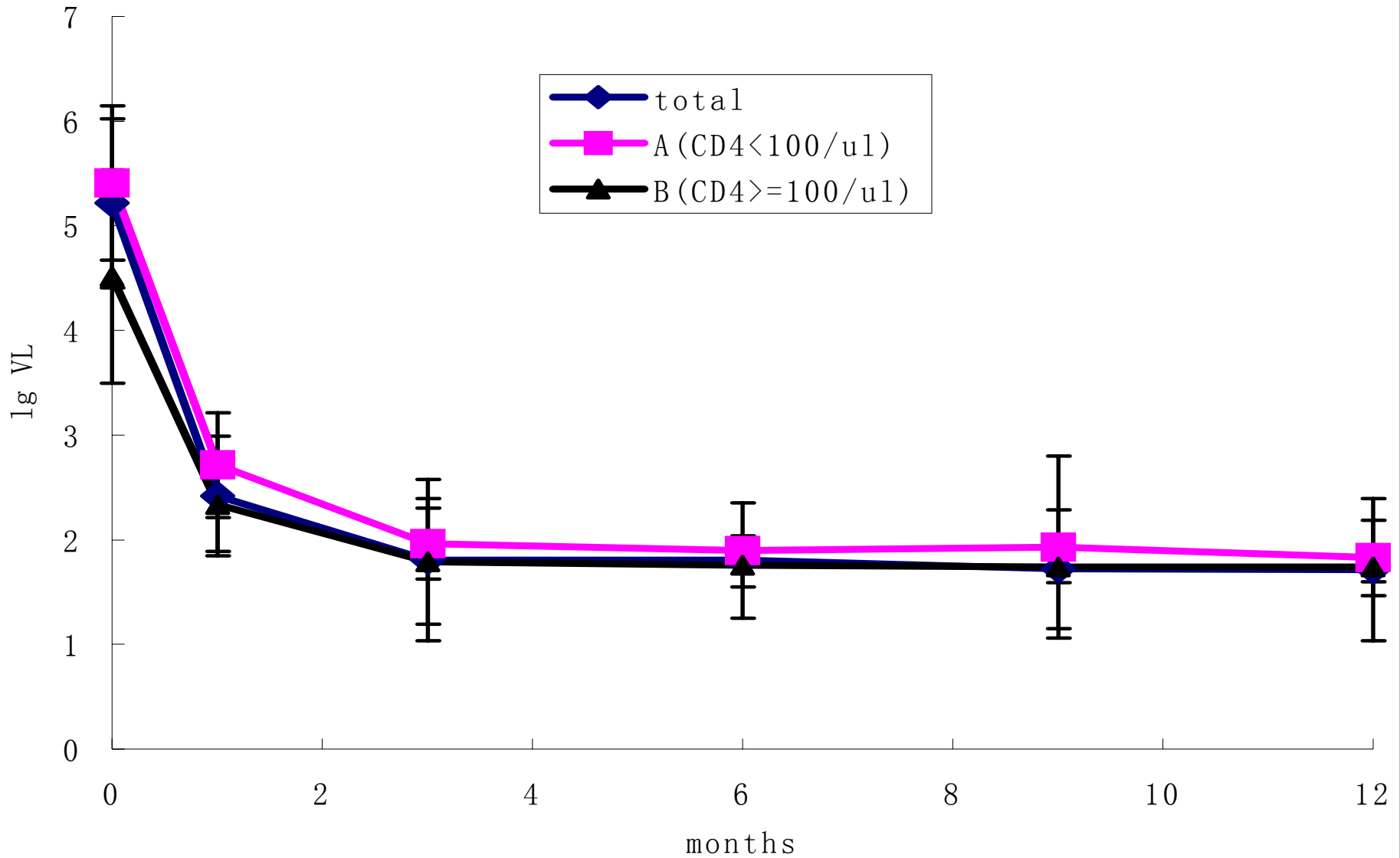
均未见新发的机会性感染

The toxicity related with HAART

103例患者在12个月HAART过程中共有39例患者发生57例次的治疗相关不良反应

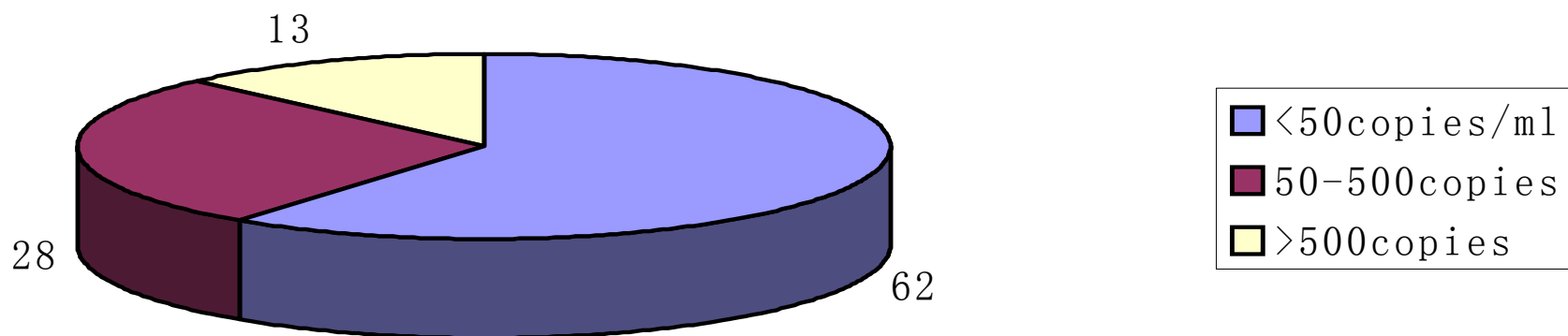


Dynamics of VL during HAART



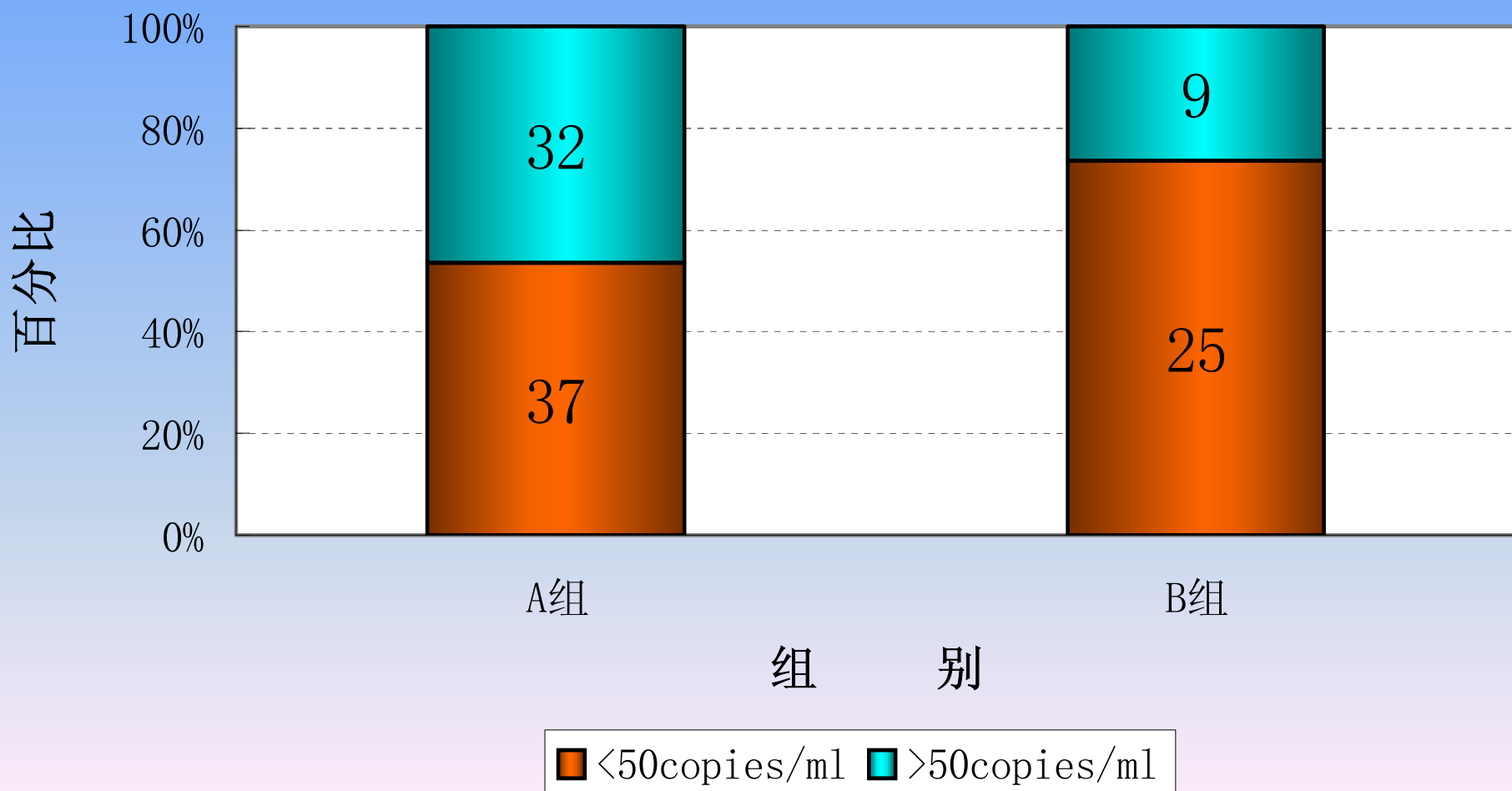
HAART12个月后血浆VL的范围

总例数 n=103

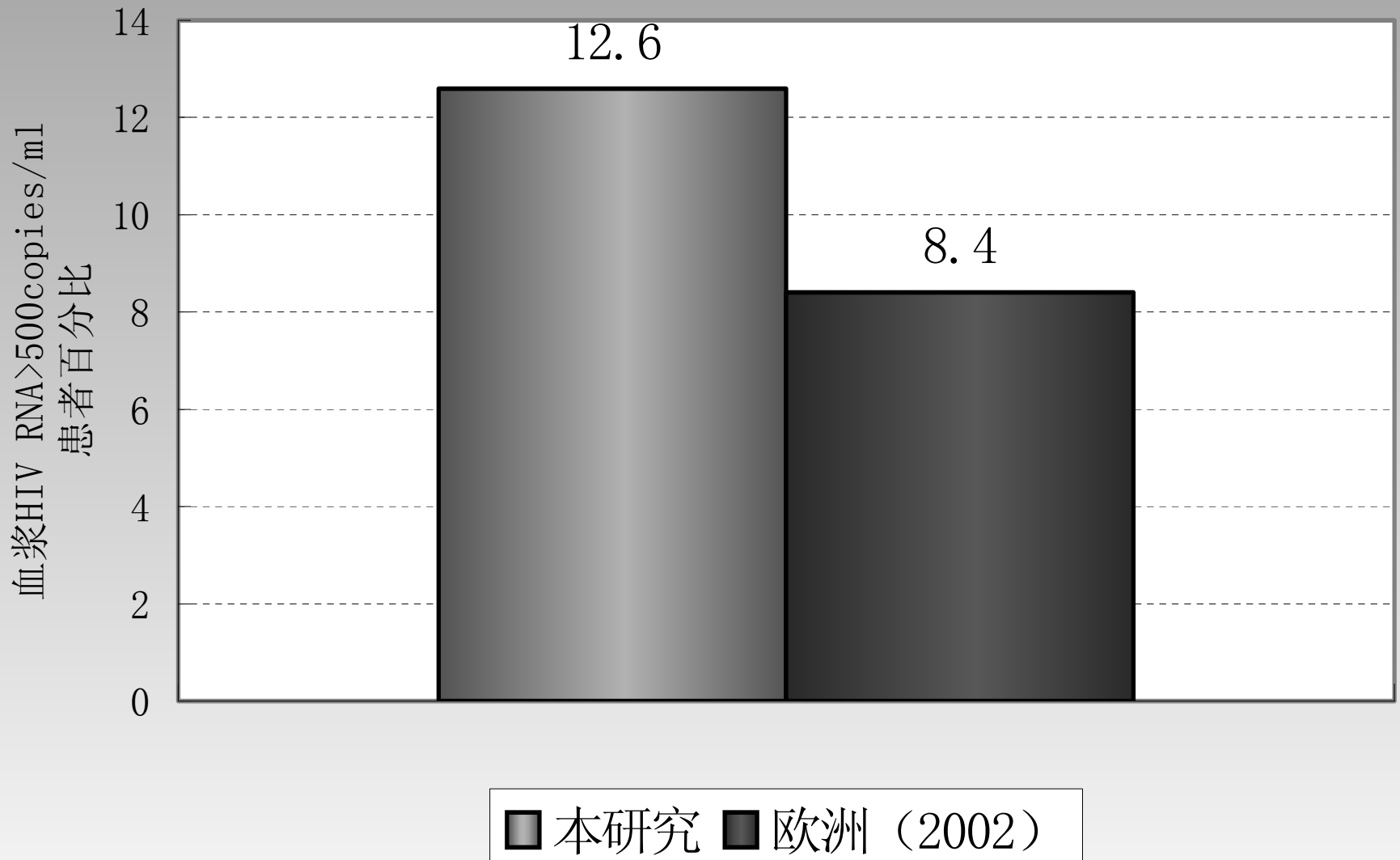


Comparing of VL change between two groups

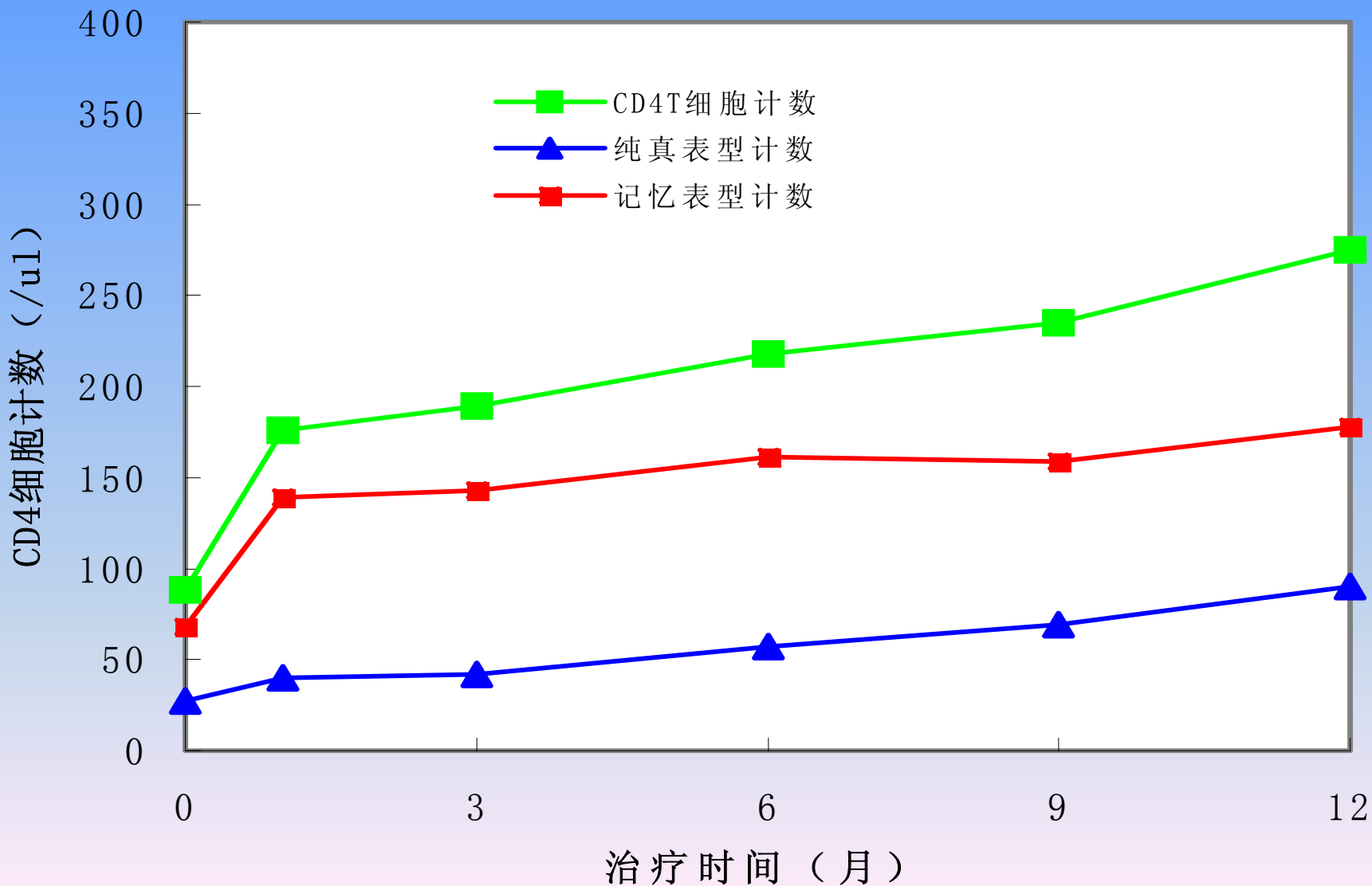
12个月HAART后血浆病毒载量



Comparing of VL change with other Euroupp report

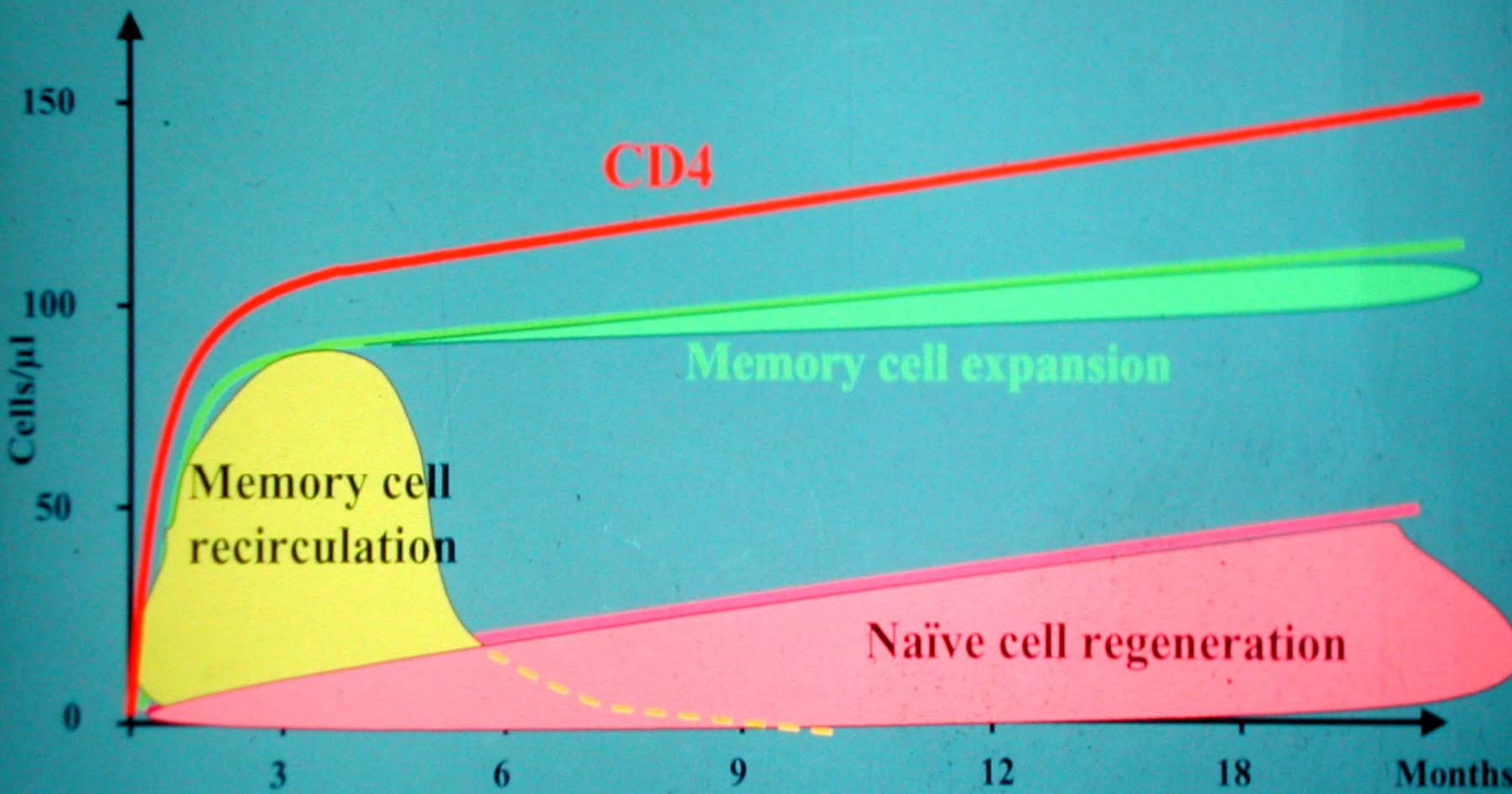


HAART12个月中CD4T细胞及其naïve和memory计数变化规律 (n=103)

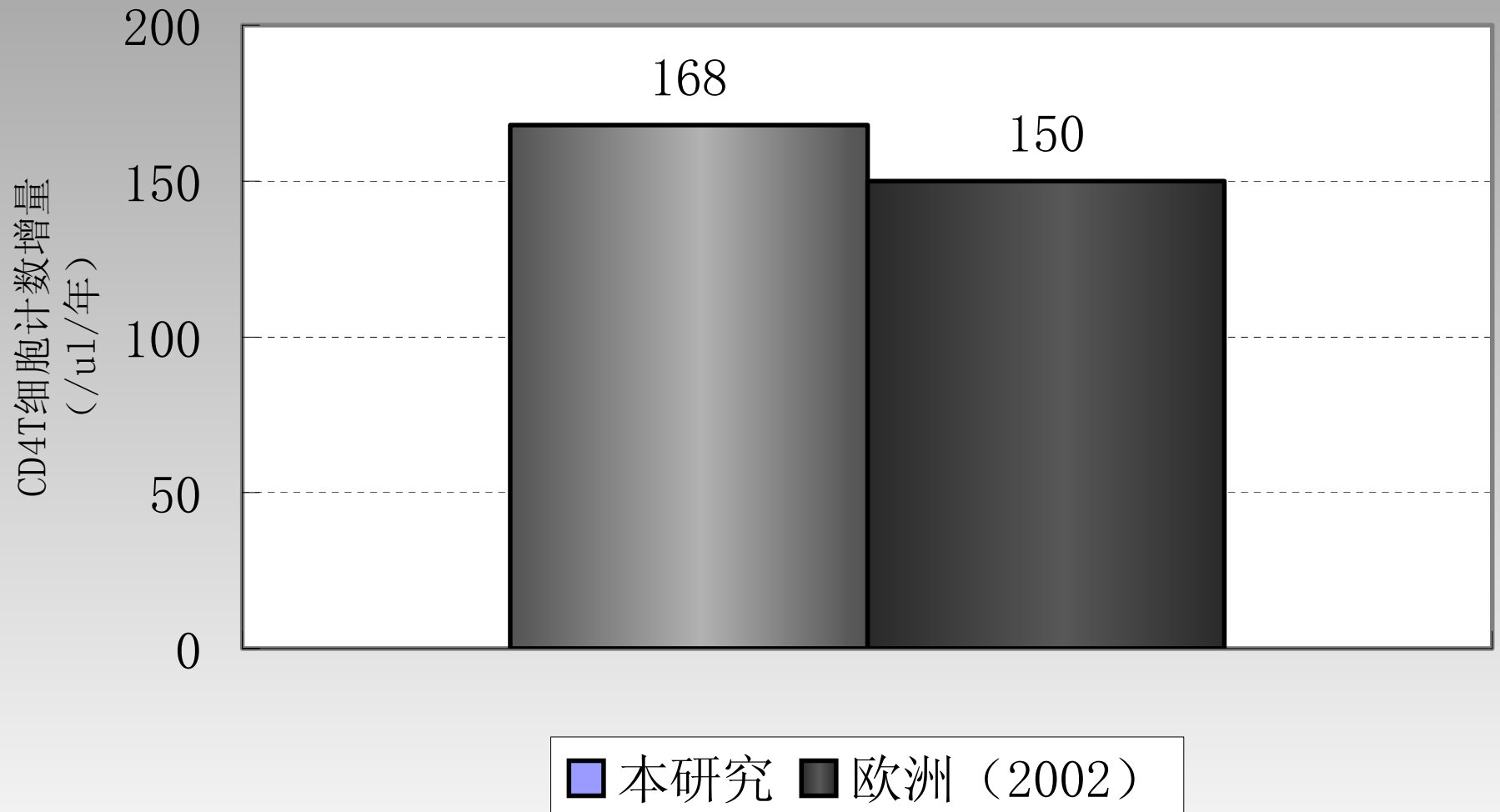


2 or 3 mechanisms of CD4 T cell reconstitution ?

early memory cell redistribution,
long term naïve cell regeneration and
late memory cell expansion ?



Comparing of the CD4 count increase after one year of HAART between our study with other report



*Lampe S, Gatell J, Staszewski S, et al. Trends over time in initial virological failure of first HAART, 1996 to 2002: a joint cohort analysis of 4143 subjects. Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Massachusetts. Abstract 593.

基本情况

临床结果

病毒学结果

CD4T变化

CD4CD28

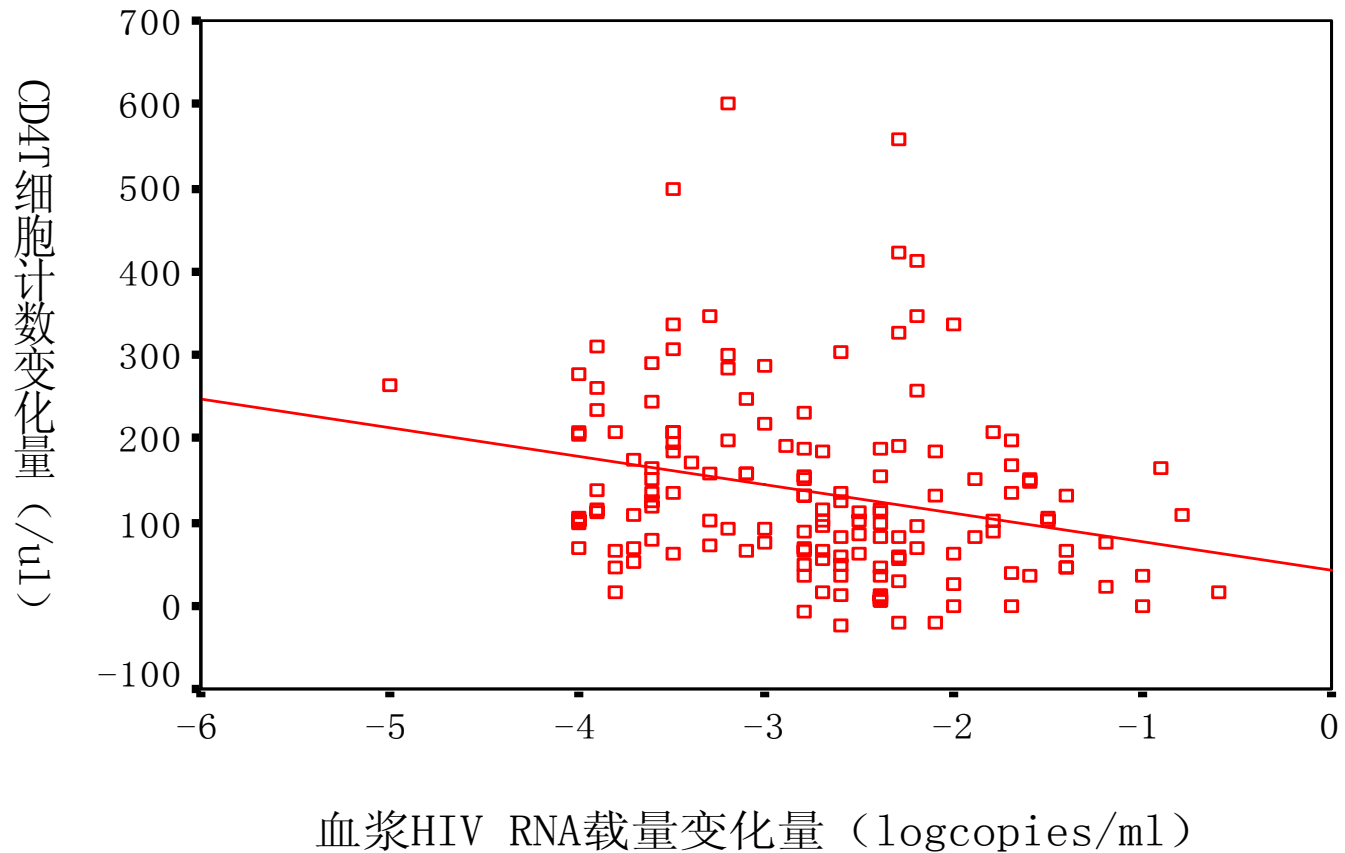
CD8T变化

淋巴细胞

Significance relation between CD4 cell increase and VL reduced after one year HAART

HAART后CD4T细胞计数变化量与血浆HIV RNA变化量间相关性分析

$r = -0.303, p < 0.001$



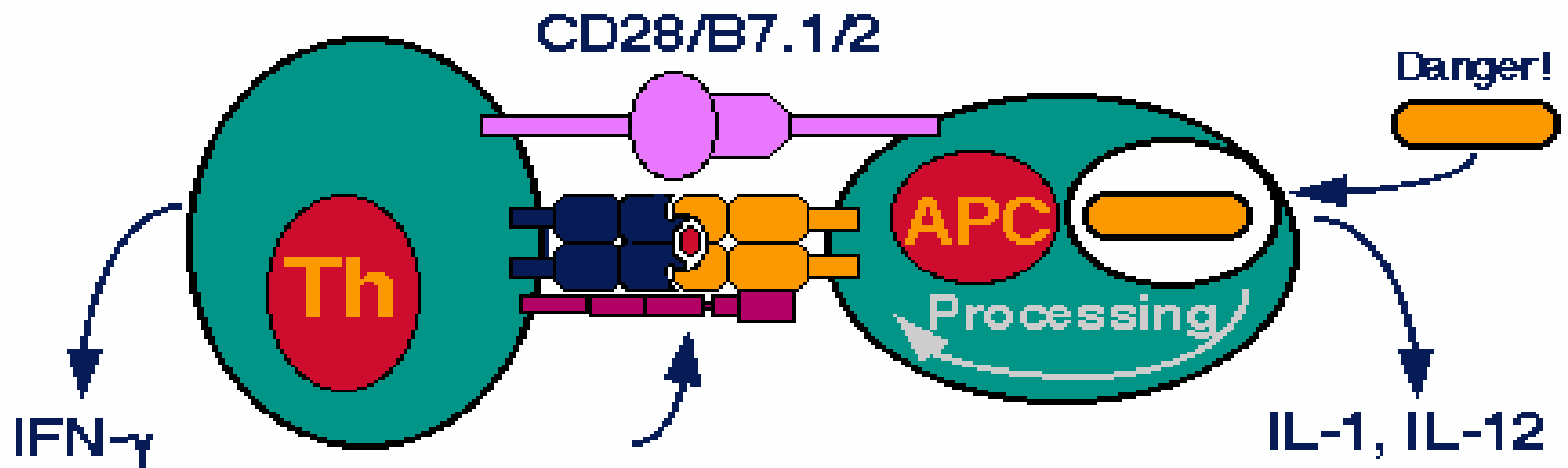
Δ CD4T without relation with baseline CD4 count and VL after HAART

	12个月HAART Δ CD4T细胞
Baseline VL	$r=0.165, p=0.410$
Baseline CD4 count	$r=-0.19, p=0.657$

Co-stimulation of T helper cells by professional APC

SIGNAL 2

Cognate T-professional APC co-stimulatory interaction

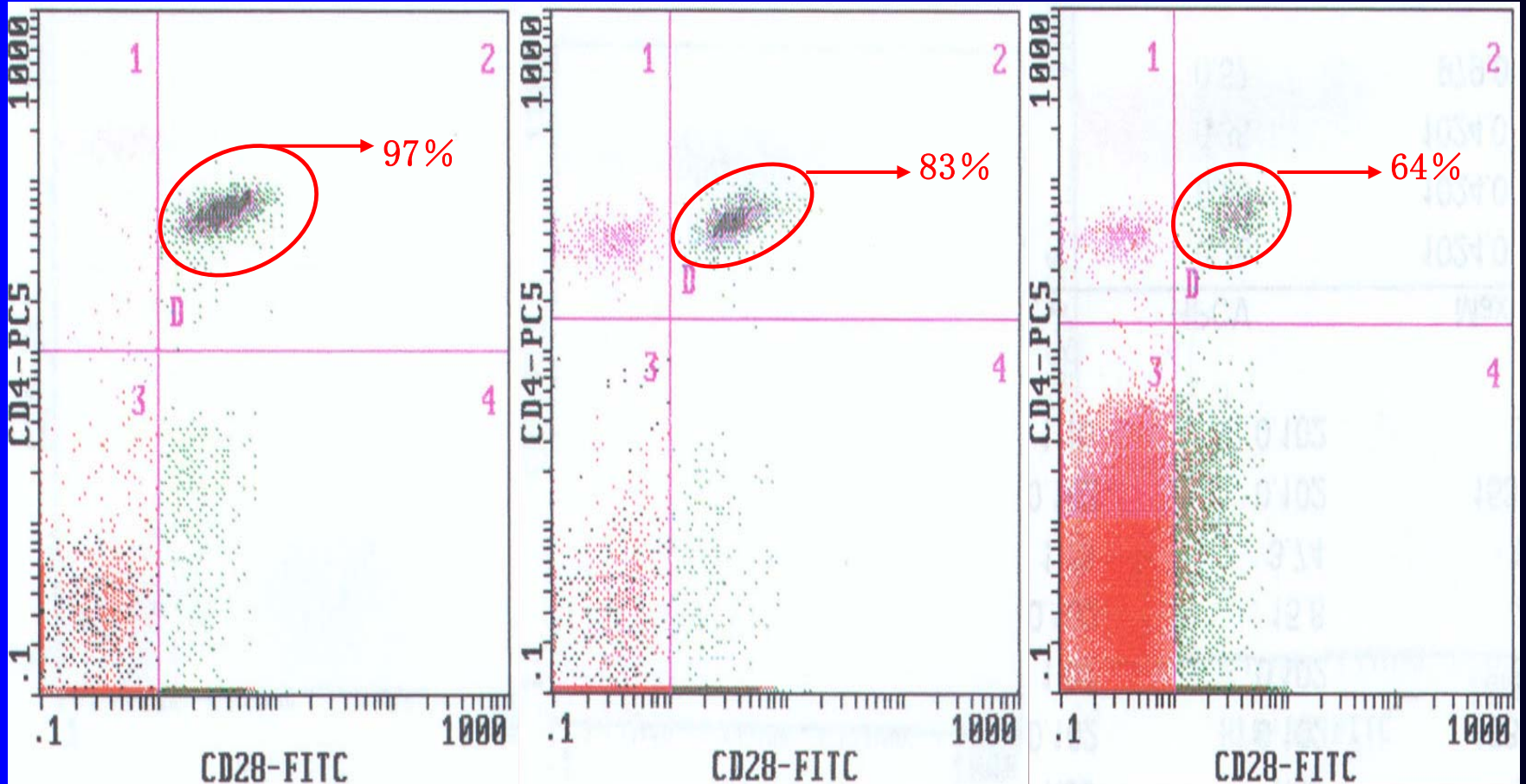


SIGNAL 1

Antigen recognition
& co-receptor ligation
induces CD28 on T cells

Signal 1 & signal 2 are required for T cell clonal proliferation and differentiation to effector cells

CD4+CD28+功能亚群比例的改变

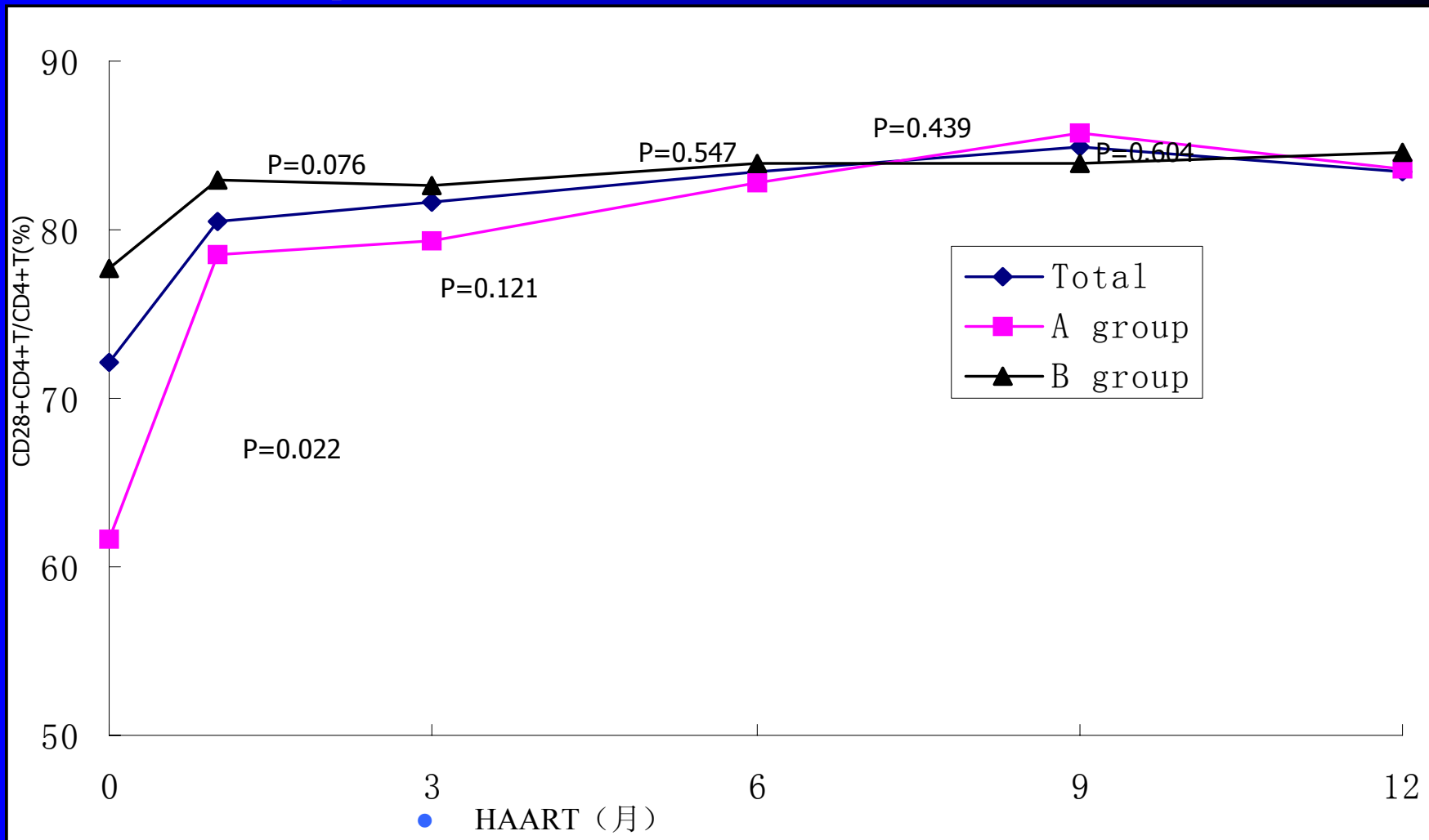


**Health
donnor**

HIV+

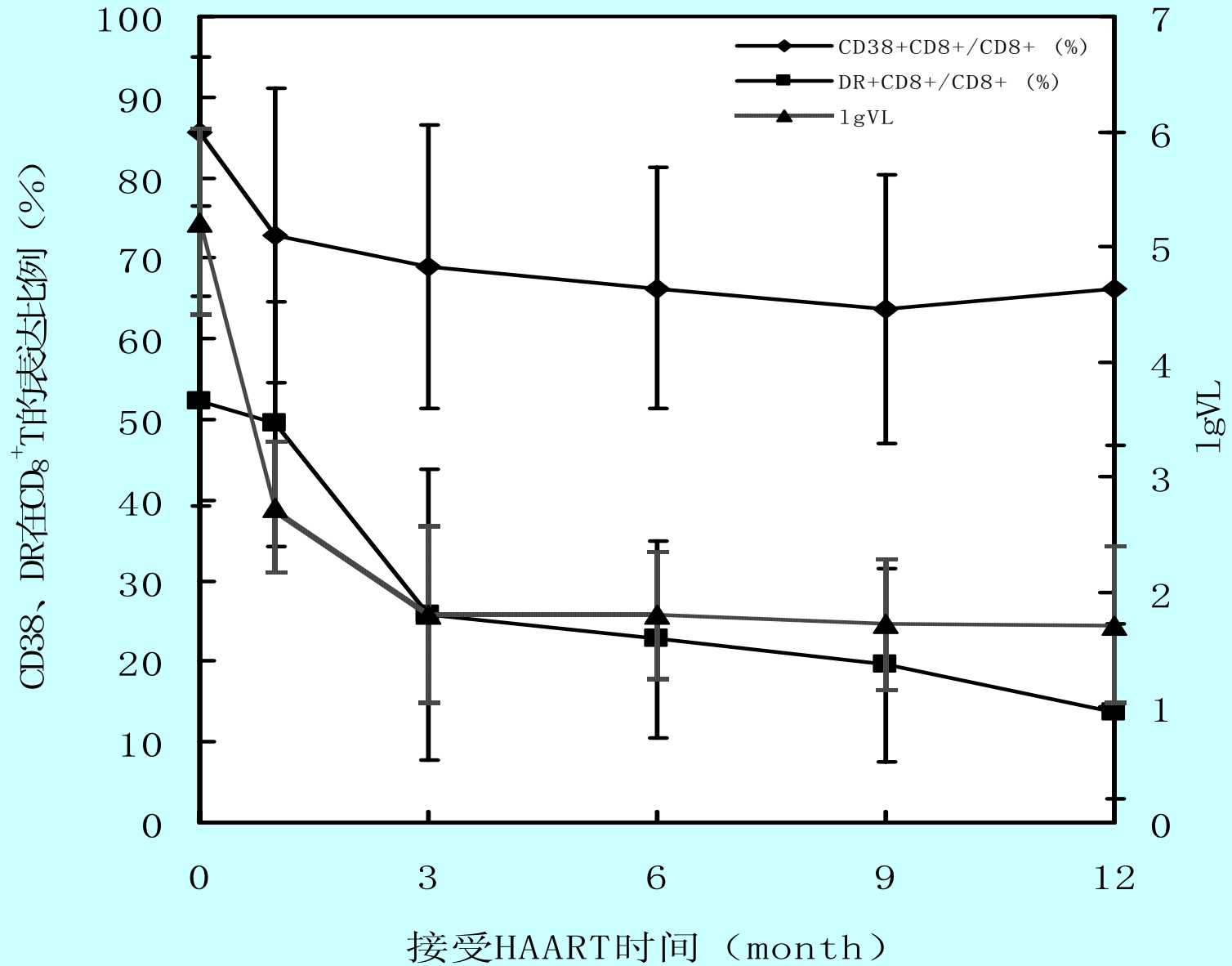
**AIDS
patient**

Significance increase of CD4CD28 expression after HAART

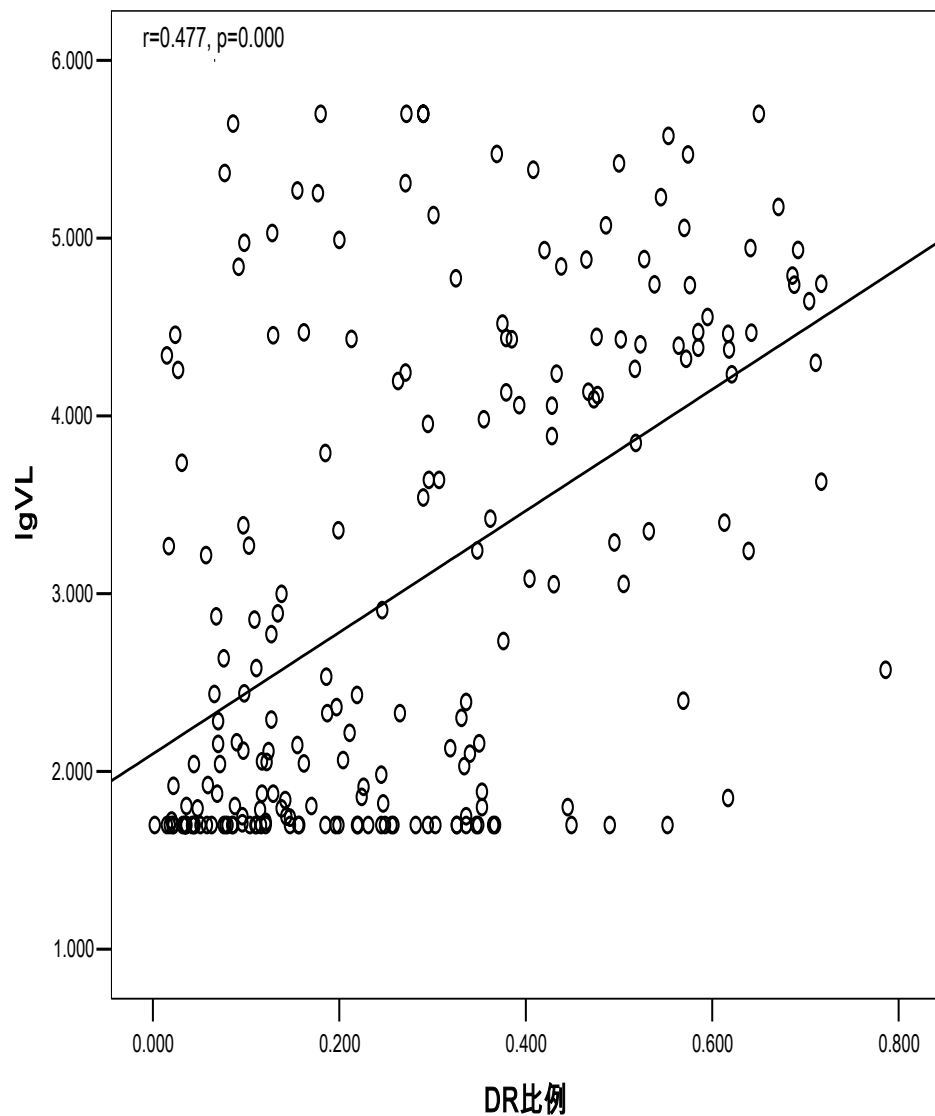
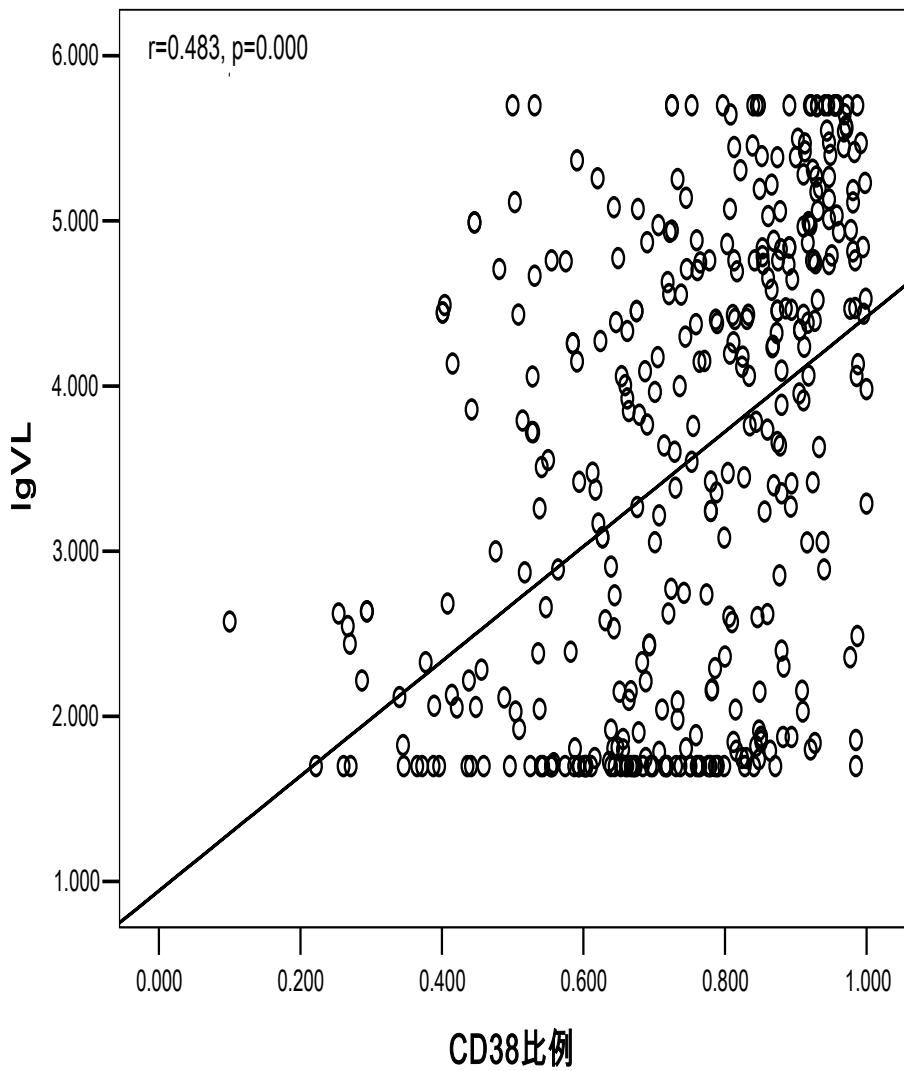


----p值是A组和B组在不同时间点比较的统计学结果

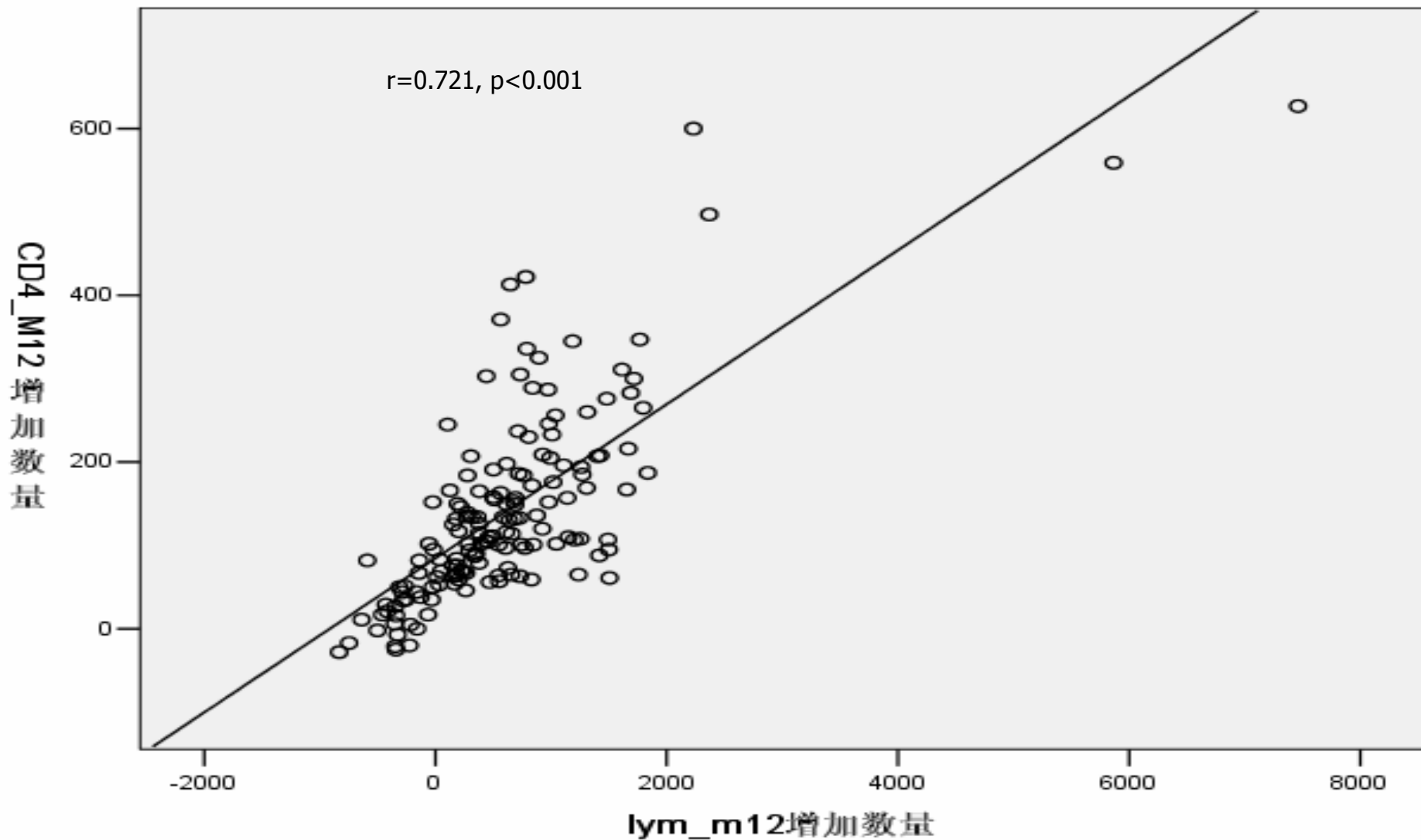
Dynamics of CD8+ subsets activation percentage and VL after HAART



Significance relation between CD8 activation and VL



HAART12个月后增加的淋巴细胞数与增加的CD4T细胞数呈显著正相关 (n=103)

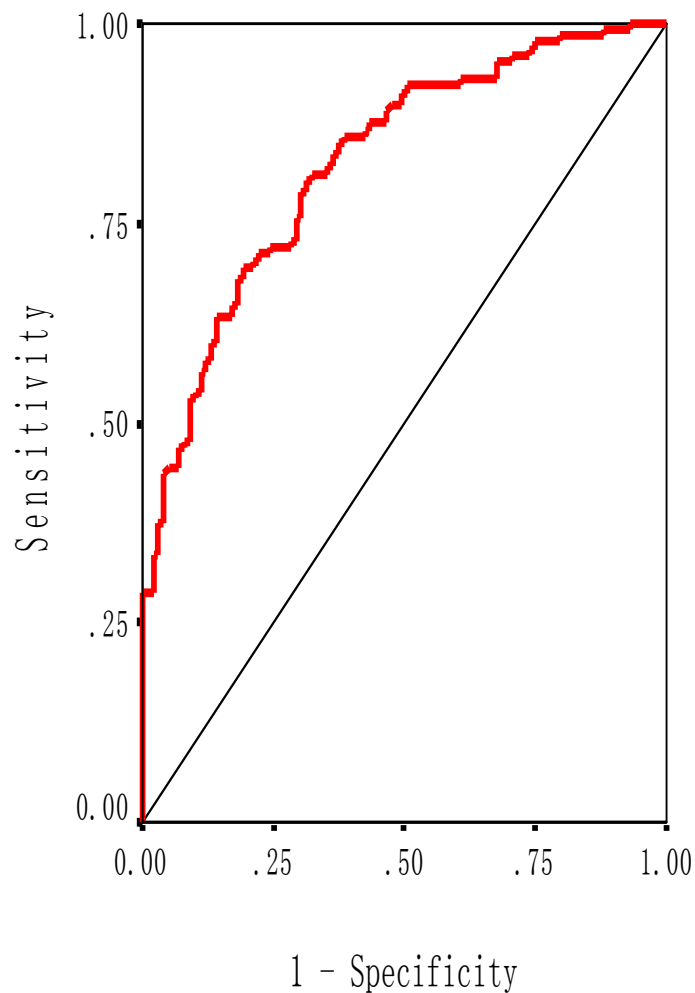


ROC曲线 (relative operating characteristic curve)

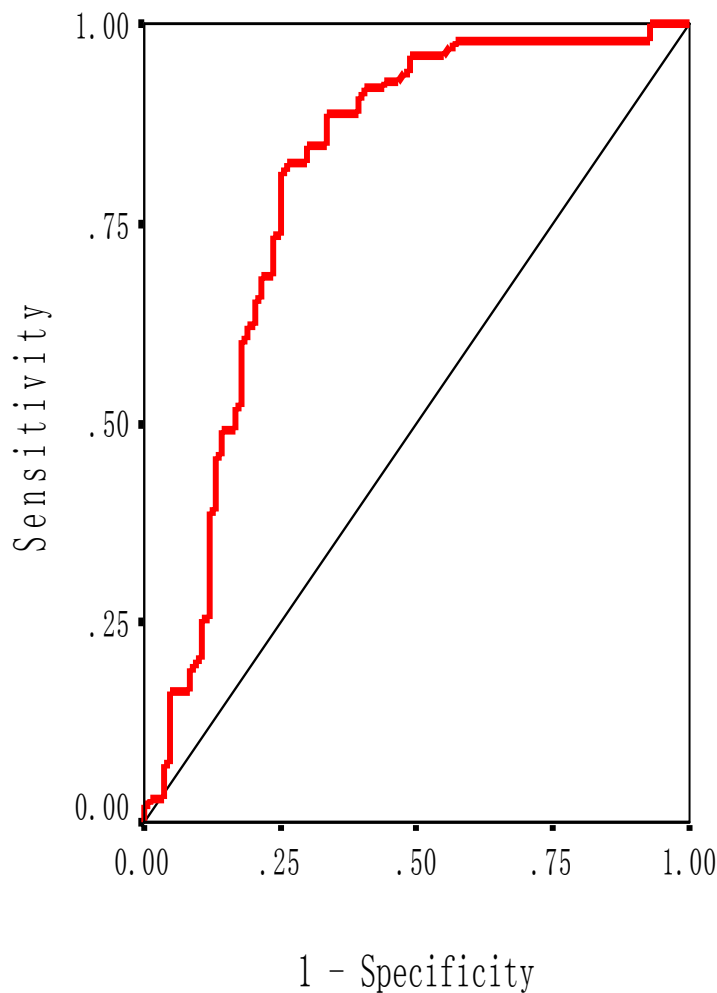
总淋巴细胞数预测CD4T细胞 $>200/u1$

Δ TLC预测 Δ CD4T细胞 $>100/u1$

用淋巴细胞总数预测CD4T细胞计数 $<200/u1$ 的ROC曲线



用总淋巴细胞变化量预测CD4T细胞增长 $>100/u1$ 的ROC曲线



在HAART的不同时间用 Δ TLC预测 Δ CD4+T的诊断价值 (n=103)

HAART治疗时间	预测CD4+T细胞增加数 (个/ul)	ROC面积 (准确性)	P 值	总淋巴细胞增加数的CUTOFF值 (个/ul)	灵敏度 (%)	特异性 (%)	阳性预测值(%)	阴性预测值(%)
M1	Δ CD4+T>50	0.964±0.032	0.000	>190	92.9	91.7	95.5	88.5
	Δ CD4+T>100	0.900±0.064	0.003	>390	85.0	83.3	82.2	79.6
M6	Δ CD4+T>50	0.903±0.026	0.000	>260	90.7	80.4	93.6	82.9
	Δ CD4+T>100	0.889±0.076	0.002	>360	93.7	90.0	91.7	89.3
	Δ CD4+T>150	0.808±0.072	0.002	>450	73.1	76.9	74.4	81.4
M12	Δ CD4+T>100	0.928±0.040	0.000	>400	84.6	90.6	84.7	91.2
	Δ CD4+T>150	0.894±0.062	0.000	>690	86.0	91.8	91.3	88.7

用**CD38**和**DR**比例预测血浆病毒载量的拷贝数

	预测病毒载量值 (拷贝/ml)	ROC面积	P 值	检测CUTOFF 值 (%)	灵敏度 (%)	特异性 (%)
CD38	VL<50	0.738±0.029	0.000	<68.5	77.1	74.8
	VL<500	0.742±0.025	0.000	<72.5	72.5	73.6
	VL>1000	0.749±0.025	0.000	>77.5	71.8	68.9
	VL>10000	0.747±0.026	0.000	>82.0	76.3	67.5
DR	VL<50	0.699±0.039	0.000	<21.0	66.7	66.3
	VL<500	0.776±0.033	0.000	<27.0	76.1	71
	VL>1000	0.797±0.033	0.000	>39.5	77.6	72
	VL>10000	0.783±0.036	0.000	>46.5	72.1	69.6

用**CD38**的比例来预测低拷贝数病毒载量（VL<50拷贝/ml和VL<500拷贝/ml）时有较高的灵敏度和特异性；而**DR**的结果在预测高拷贝数病毒载量（VL>1000拷贝/ml和VL>10000拷贝/ml）时表现出更高的灵敏度和特异性。

Conclusions

1. 103例HIV/AIDS患者经12个月HAART后获得了显著的临床、病毒学及细胞免疫学疗效；
2. **CD4T**细胞增长呈双相过程，早期以记忆表型快速增长为主，后期以纯真表型的缓慢增长为主；
3. 决定免疫重建的最主要因素是病毒复制被控制；
4. 淋巴细胞总数和 T 细胞激活亚群检测有希望作为替代指标，在条件匮乏地区作为**HAART**疗效评估的指标

Conclusion

HAART能成功的重建
中国艾滋病病人的免疫功能



北京协和醫院